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## REMARKS

The Applicants thank the Examiner and her Supervisor for their time and courtesy during the personal interview at the US Patent and Trademark Office on April 18, 2005.

Claims 1-16 are pending in the case. Claim 8 is objected to for being in improper dependent form. Claims 1, 2, 5-8 and 11-16 are rejected under 35 USC 112, first paragraph for failing to comply with the enablement requirement. Claims 3, 4, 9 and 10 are objected to as being dependent on rejected claims. Claims 1-11 are rejected under the judicially created doctrine of obviousness type double patenting. Claims 1, 6 and 12 are amended. The amendments are supported on page 122, lines 6-9. Claims 2, 8, and 13 are cancelled.

The Applicants have amended the claims as set forth above and submit that in view of the forgoing amendments and following arguments that the claims are now in a proper form for allowance.

### I. Claim rejections under 35 USC 112, paragraph 1

The Examiner has rejected claims 1, 2, 5-8 and 11-16 under 35 USC 112, paragraph 1 for failing to meet the enablement requirement. Claims 3-4 and 9-10 are not included in the rejection; therefore, they must be enabled by the specification.

Claims 3-4 and 9-10 include the limitations that either one or both of the sterol moieties be cholesterol. The Applicants submit that the properties of sterols are well known to those skilled in the art. Moreover, it has been demonstrated that the addition of any of a number of sterol moieties to an oligonucleotide has substantially the same effect on the melting temperature of the oligonucleotide to its complement as shown in Table 2 on page 319 of *Antisense Research and Applications* (Eds. ST Crooke and B Lebleu, 1993, copy enclosed). As antisense oligonucleotides function by hybridizing to their target sequence and modification of an oligonucleotide with a sterol moiety does not

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interfere with this binding, one would have a reasonable expectation that an oligonucleotide modified with cholesterol moieties would function similarly to an oligonucleotide modified with other sterol moieties (e.g. digoxigenin, cholic acid). Therefore the rejection under 35 USC 112, paragraph 1 for lack of enablement of claims 1, 2 and 5-7 is traversed.

The Examiner points to the Letsinger reference to demonstrate the unpredictable nature of oligonucleotides in the inhibition of gene expression and the treatment of disease. The Applicants submit that the claims of the instant application are drawn to the use of antisense oligonucleotides. It is unlikely that the oligonucleotides of Letsinger are functioning by an antisense mechanism as stated in the final sentence of the abstract which states, "There facts, and the finding that the activity of the phosphorothioate decamers does not correlate with specific sequence, suggests that a mechanism other than "antisense inhibition" may be operative in this system." Per the statements of Letsinger, the teachings of the reference are not relevant to the claims of the instant application.

A number of sterol conjugated antisense oligonucleotides have been demonstrated to function in both *in vitro* and *in vivo* assays as reviewed in *Antisense Drug Technology* (Ed. ST Crooke, 2001, pp. 394-407 copy enclosed). A number of different targets are discussed including ICAM, ras, raf, PKC-alpha, CYP2B1, HCMV, p75 and HIV-1. The Applicants submit that these data support the broad use of cholesterol conjugated antisense oligonucleotides as claimed in the instant invention.

## **II. Double patenting rejection**

The Examiner has rejected claims 1-11 for obviousness-type double patenting over claim 2 of US Patent No 6,753,423. The Applicants submit that the rate of clearance of the oligonucleotide containing two modifications is not obvious in view of claim 2 of the '423 patent. Therefore the rejection is traversed.

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The second double patenting rejection in view of US Patent Application 2004/0142899 is a provisional double patenting rejection. The Applicants request that this rejection be held in abeyance until allowable matter is identified in one of the cases.

### III. Fees

The Applicants hereby request that the Commissioner charge Deposit Account No. 50-0252 the fee of \$225.00 for an extension in time of reply of two (2) months, small entity. It is believed that no further fee is due. However, if an additional fee is due, the Commissioner is hereby entitled to charge the fee to the Deposit Account listed above citing Reference No. ISIS-5028.

### IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, an early office action on the merits of the case is respectfully requested.

Respectfully submitted,



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Enclosures: 2 references, 14 pages total